

## REMARKS

Claims 1 and 9 are pending in the application. No new matter is added.

In support of the remarks and arguments stated *infra*, Applicants have submitted herewith the Declaration of Dr. Jonathan S. Stamler under 37 C.F.R. §1.132 ("Stamler Declaration").

### Rejection under 35 U.S.C. §103

Claims 1 and 9 are rejected under 35 U.S.C. §103(a), as being unpatentable over U.S. Patent 6,331,543 to Garvey ('543) in view of U.S. Patent 6,314,956 to Stamler ('956) and further in view of U.S. Patent 5,380,758 to Stamler ('758). *See*, Office Action at pages 2-9.

Pending claims 1 and 9 require that the compositions be "administered to the nasal mucosa and osteomeatal complex." The '543 patent teaches that the disclosed compounds (*e.g.*, *S*-nitrosothiols) can be administered as a powder and administered by inhalation spray. The '956 patent teaches that the disclosed compounds (*e.g.*, ethyl nitrite) can be administered as a gas and administered by inhalation. The '758 patent teaches that the disclosed compounds (*e.g.*, *S*-nitrosothiols) can be administered as an aerosol. As such, administration to the nasal mucosa and osteomeatal complex is not taught or suggested by the combination of the '543, '956 and '758 patents. However, the Examiner has previously stated that inhalation as taught by the prior art references would have included the mouth as well as the nose. *See*, Office Action mailed January 31, 2006 at page 5. Applicants traverse.

Applicants submit that one of ordinary skill in the art would readily recognize a distinction between administration by inhalation and administration to the nasal mucosa and osteomeatal complex. Specifically, the ordinary skilled artisan would recognize that inhalation serves as a route of local administration of a composition or drug to the lungs. The presently claimed invention allows for the systemic delivery of the claimed compositions through absorption by the nasal mucosa and osteomeatal complex which differs from the local administration to the lungs via inhalation taught by the combination of the '543, '956 and '758 patents. *See*, Stamler Declaration ¶ 6.

Administration to the nasal mucosa and osteomeatal complex provides numerous advantages over other systemic delivery methods, such as parenteral and oral administration, including: non-invasiveness, efficient absorption via highly-vascularized mucosa, rapid onset of action, improved compliance, avoidance of any degradation and/or unwanted metabolism of the

drug, which can change the drug's molecular structure and potential for direct delivery to the brain via the tight junctions present in the nasal mucosa and osteomeatal complex. *See*, Stamler Declaration ¶ 7.

Further, another advantage of administration of composition or drug to the nasal mucosa and osteomeatal complex is that, typically, a much lower actual dose of the composition or drug can be administered because, compared to oral dosing, the first pass metabolism in the liver and gastrointestinal tract is avoided. *See*, Stamler Declaration ¶ 7. Diabetes patients, for example, could benefit from delivering insulin to the upper airways, allowing them to do away with needle injections. Nasal delivery has been shown to be essential for various compositions including: the peptide drugs PYY for obesity, PTH (parathyroid hormone) for osteoporosis, and the protein  $\beta$ -interferon for multiple sclerosis.

Additionally, administration of the claimed compositions to the nasal mucosa and osteomeatal complex in patients suffering from severe cystic fibrosis symptoms; such as, bronchoconstriction, mucus plugging in the lungs or bacterial bronchitis/brochiolitis, will provide rapid relief and will not be hindered by limitations of local delivery to the lungs via inhalation due to these severe symptoms. *See*, Stamler Declaration ¶ 7.

The advantages of the administration route of the instant invention such as the large surface area, porous endothelial membrane, high total blood flow, the avoidance of first-pass metabolism, ready accessibility and rapid systemic absorption following administration of a composition or drug to the nasal mucosa and osteomeatal complex are not taught or suggested by the by the combination of the '543, '956 and '758 patents. *See*, Stamler Declaration ¶ 8.

Thus, one of ordinary skill in the art would not be motivated to combine the teachings of the '543, '956 and '758 patents to reach the present invention.

Reconsideration and withdrawal of the present rejections is respectfully requested.

**APPLICANTS:** Gaston and Stamler  
**U.S.S.N.:** 10/772,374

### **CONCLUSION**

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance. Should any questions or issues arise concerning this application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Ivor R. Elrifi', written over a horizontal line.

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